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Laryngeal Atresia Type III (Glottic Web) With 22q11.2 Microdeletion: Report of Three Patients

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The clinical manifestations of patients with a 22q11.2 deletion are highly variable and mainly include developmental defects of structures derived from the third and fourth pharyngeal pouches. Laryngeal atresia has occasionally been reported in DiGeorge syndrome as well as in velo-cardio-facial syndrome. We observed three patients with type III laryngeal atresia (glottic web) and 22q11.2 microdeletion. One patient showed a "classical" 22q11.2 deletion phenotype with clinical overlap with DiGeorge and velo-cardio-facial syndromes. However, the pattern of congenital anomalies of the two others was less specific, heart defects and minor anomalies being the only outstanding clinical manifestations suspicious for monosomy 22q11.2. Our findings suggest that laryngeal atresia represents an additional malformation which should prompt investigation of 22q11.2 deletion, especially in combination with congenital heart defects. Am. J. Med. Genet. 70:130–133, 1997.

KEY WORDS: CATCH 22; DiGeorge syndrome; laryngeal atresia; microdeletion 22q11.2; velo-cardio-facial syndrome

INTRODUCTION

Microscopic and submicroscopic deletions of chromosome 22q11.2 cause a wide range of phenotypes including DiGeorge syndrome (DGS), velo-cardio-facial (Shprintzen) syndrome (VCFS), conotruncal anomaly face syndrome (CTAFS), and sporadic or familial heart defects. As this group of related disorders mainly affects the development of the face, conotruncus, thymus, and parathyroid glands, it can be concluded that genes on 22q11.2 play an important role in embryological development of the 3rd and 4th pharyngeal pouches. The acronym CATCH 22 (cardiac defect, abnormal facies, thymus hypoplasia, cleft palate, hypocalcemia, and chromosome 22 deletion) was coined to encompass the overlapping phenotypes [Wilson et al., 1993]. Molecular studies using fluorescence in situ hybridisation (FISH) detected microdeletions in 88% of DGS [Driscoll et al., 1993], in 81% of VCFS [Lindsay et al., 1995], and in 84% of CTAFS [Matsuoka et al., 1994]. Investigation of nine families with recurrence of congenital heart disease showed a 22q11.2 deletion in five of them [Wilson et al., 1992]. Similar studies were performed in cases of isolated conotruncal heart defects. However, the frequency of 22q11.2 deletions in this group of cardiac malformations seem to vary over a wide range [Wilson et al., 1992; Amati et al., 1995]. Laryngeal atresia was reported previously as an associated manifestation of DGS and VCFS. In four patients with Shprintzen syndrome and laryngeal web, a 22q11.2 microdeletion was observed [Driscoll et al., 1992; Lindsay et al.,1995]. We describe three further patients with type III laryngeal atresia due to a 22q11.2 microdeletion and discuss this particular malformation as a phenotypical hint for the search of a 22q11.2 deletion.

CLINICAL REPORTS

Patient 1

The first patient is a newborn girl born to nonconsanguineous parents of Swiss origin. She was the second child of a 30-year-old mother and a 35-year-old father. Both parents were healthy, and the pedigree was unremarkable. Pregnancy and delivery at 40 weeks were uneventful. Birth weight was 3,200 g (10th–50th centile), birth length was 52 cm (50th–90th centile), and head circumference (OFC) was 34 cm (50th–90th centile). Shortly after birth, the infant presented with aphonia, expiratory stridor, cyanosis upon stimulation, and a systolic cardiac murmur. Echocardiography and heart catheterisation disclosed a perimembranous ventricular septal defect and a right-

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sided aortic arch. Laryngoscopy performed at 3 days of life revealed a thick anterior glottic web, leaving a rest airway lumen of about 1/4 and a fibromuscular subglottic stenosis with involvement of the cricoid. The proposita also had bilateral choanal stenosis. Endoscopic dilatation of the laryngeal stenosis failed, and a long-term tracheostomy had to be performed. At age 3 months, she underwent cardiac surgery. Severe gastroesophageal reflux necessitated a fundoplication and gastrostomy at age 4 months. The patient had a round face with bilateral inner epicanthic folds, slightly upslanting palpebral fissures, full cheeks and a small mouth (Fig. 1). Her fingers appeared long and tapering, and she had proximally implanted thumbs. Motor and cognitive development at 5 months of life was appropriate for age. Calcium blood levels were normal (2.53 mmol/l at 1 month), as were results of the following immunological investigations: IgG including subclasses, B + T cell count and distribution, adhesion molecules, and cell proliferation on mitogens.

Patient 2

This girl is the first child of healthy unrelated parents. The mother was 35 and the father 46 years old at her birth. Family history is unremarkable. The proposita was delivered through cesarian section at 39 weeks of an uneventful pregnancy. Birth weight (2,450 g) was below the 10th centile, birth length (49 cm) was at the 50th centile, and OFC (32 cm) was between the 10th and 25th centile. Neonatal evaluation showed a mewing, high-pitched cry, hypotonia, and a systolic heart murmur, due to a perimembraneous ventricular septal defect. These findings suggested the diagnosis of cri-du-chat syndrome. However, cytogenetic analysis using GTG-banding techniques showed a normal female karyotype without any structural abnormalities of chromosome 5, and FISH examination excluded a microdeletion within the critical cri-du-chat region on 5p. Because of the persistent weak and high-pitched cry, laryngoscopy was performed at 8 months of life. This examination showed a glottic web of the anterior 2/3 of the vocal cords and a subglottic fibrous stenosis without involvement of the cricoid. Reevaluation at the same time showed a round face with full cheeks, a small "carp-shaped" mouth with downturned corners (Fig. 2) and a high-vaulted palate. The fingers appeared long and tapering, and she had overlapping toes with bilateral clinodactyly of the fourth toes. At 8 months, her weight was between 10th and 25th centile, her length was at the 50th centile, and her OFC was at the 3rd centile. Recurrent episodes of dyspnea with every upper respiratory tract infection, as well as persistent dysphonia required an endoscopic laser treatment of the glottic web at 3 years. On chest X-ray examination a thymus was visualized. In absence of any symptoms of immunodeficiency no immune function tests were performed. Psychomotor development was normal: the proposita walked at 17 months, started to use single words between 18 and 24 months, and made two words sentences at 26 months.

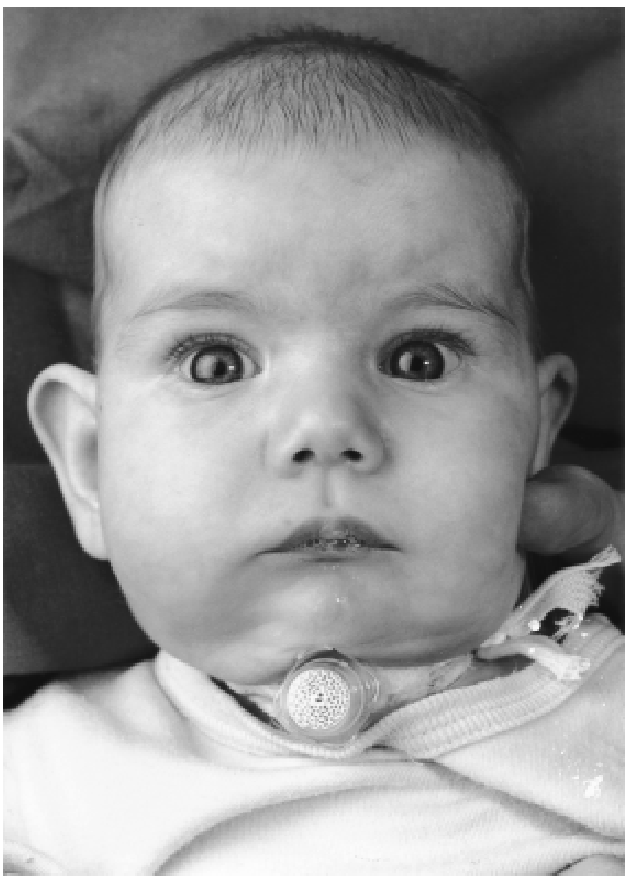

Fig. 1. Patient 1 at age 5 months.

Patient 3

The third patient was a 11.5-year-old girl. She is the fourth daughter of unrelated parents both 36 years at her delivery. The mother, maternal grand-mother, and three older sisters have idiopathic thrombocytopenia. The patient was delivered by caesarian section at 39 weeks. Birth weight was 4,000 g (> 90th centile), length was 50 cm (50th–90th centile), and OFC was 35 cm (almost 90th centile). Initial evaluation demonstrated tetralogy of Fallot with a single right pulmonary artery, transient hypocalcemia neonatally, a peribuccal angioma, and an anterior glottic web, which was corrected at 5 days. Minor facial anomalies were not recorded at birth. She sat at 4 months, walked at 17 months, and said single words at 18 months. Growth development was normal. At 23 months, she underwent complete repair of the heart defect. During surgery, a hypoplastic thymus was found, and DGS was diagnosed. However, at 11.5 years the patient had minor anomalies more compatible with the VCFS, including a long face, down-slanting and narrow palpebral fissures, hypoplastic alae nasi, prominent nose with a squared nasal root, malar flatness, mouth often held open (Fig. 3), arched palate, and hypernasal speech. The fingers appeared long and tapering.

METHODS AND RESULTS

Cytogenetic analysis using GTG-banding at a 400 band level failed to show an interstitial deletion of

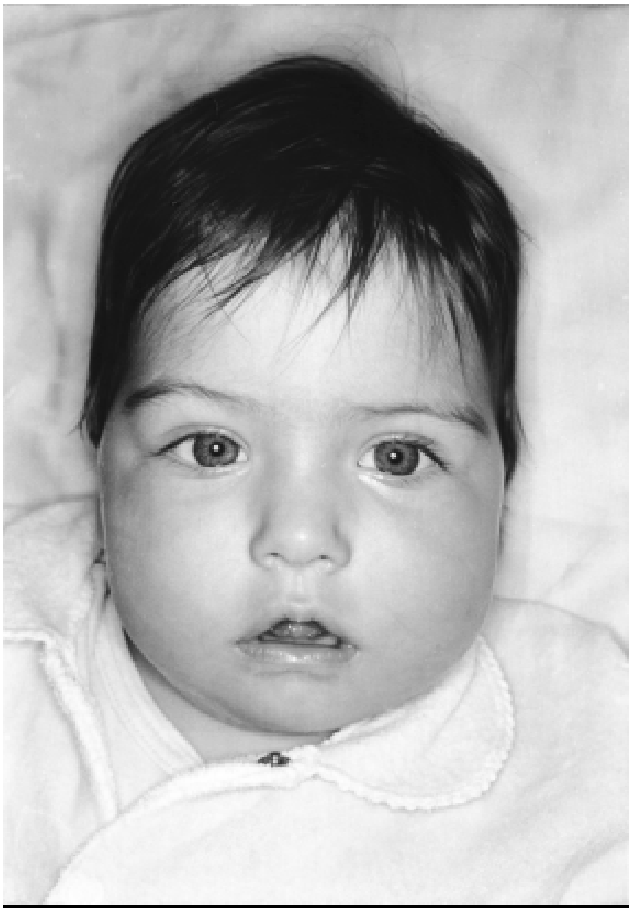

Fig. 2. Patient 2 at age 8 months.

Fig. 3. Patient 3 at 11½ years of age.

chromosome 22q11.2 in any of the reported patients. FISH of metaphase chromosomes with the cosmid probe D22S502 (DO832) [Lindsay et al., 1993] at 22q11.2, and a control probe D22S326 (CDAC9), located at the distal long arm of chromosome 22, were performed. The cosmid probe D22S502 maps telomeric to the DiGeorge critical region within the commonly deleted region. The FISH analysis showed a submicroscopic deletion in all three patients. No microdeletion was detected in the parents.

DISCUSSION

Congenital glottic webs as described in the three patients represent the mildest form of laryngeal atresia. Based on the severity and location of the malformation, laryngeal atresia can be classified into three types. This classification was first proposed by Smith and Bain [1965] and then revised by Zaw-Tun [1988]. The larynx develops from endoderm of the cranial part of the laryngotracheal groove as well as from mesenchyme of the fourth, fifth, and sixth branchial arches. From about the 6th week of embryonic life, proliferating epithelium temporarily obliterates the developing laryngeal opening. An autolytic process reestablishes the lumen by the 10th week of gestation. Each type of laryngeal atresia represents a developmental arrest at a different stage of this recanalisation. Arrest in development before the end of the 7th postovulatory week causes type I lesions. These are the most severe ones with atresia of the entire larynx. Arrest in the 8th and beginning of the 9th week leads to laryngeal atresia type II, which consists of a supraglottic obstruction, separating an incompletely formed vestibule from the infraglottic part. Type III atresia is a partial obstruction of the glottis by a membranous web and arises when the dissolution of the remnant epithelium at the level of the vocal folds does not succeed by the end of the 9th week. This so-called "glottic" type seems to be the most common one [Zaw-Tun, 1988]. Independent of the web, an additional subglottic stenosis due to maldevelopment of the cricoid may occur in laryngeal atresia type III [Cohen, 1985].

The clinical manifestations of laryngeal atresia type III in the neonatal period include abnormalities of the cry, stridor, and/or respiratory distress due to severe airway obstruction [Benjamin, 1983]. Diagnosis is made by laryngoscopy. For type III laryngeal atresia, appropriate treatment can be given, whereas types I and II are invariably fatal unless tracheostomy is performed immediately after birth.

Laryngeal atresia is often associated with other congenital anomalies, yet without any consistent pattern. Zaw-Tun [1988] mentioned that the likelihood of serious associated malformations is probably greatest with type I laryngeal atresia, somewhat less with type II, and least with type III (most of which are treatable). Reports of associated cardiovascular anomalies were published by several authors. Shearer et al. [1972] described three patients with congenital laryngeal web

and ventricular septal defect. Gay et al. [1981] reported on a patient with the combination of laryngeal web, congenital heart disease, and short stature. In a series of 29 patients with congenital laryngeal web, Benjamin [1983] found 2 with cardiac defects: 1 had a complex heart defect and the other a tetralogy of Fallot. In Cohen's [1985] series of 51 patients with laryngeal web, there were six cases with a heart defect (two with ventricular septal defects, one with double aortic arch, one with pulmonary artery stenosis, one with tetralogy of Fallot, and one with patent ductus arteriosus). There are also a few reports where the clinical findings are compatible with the DiGeorge syndrome. Miller et al. [1984] documented thymic aplasia in a patient with laryngeal atresia type I. Woo and Kamody [1993] described a case with laryngeal atresia type II, associated pseudotruncus, and hypocalcemia, and Moermann et al. [1992] reported laryngeal atresia type I in a case classified as DGS (with severe hypoplasia of the thymus and hydrops, but no cardiovascular malformations). In these patients with DGS no determination of a 22q11.2 microdeletion was carried out. Among 15 patients with Shprintzen syndrome, Driscroll et al. [1992] observed one who in addition showed a laryngeal web and psychiatric illness. Molecular studies by quantitative Southern blot analysis detected a deletion of 22q11.2 in this patient. In Lindsay's [1995] series of 54 patients with VCFS, there were three with additional laryngeal web. All three patients showed a 22q11.2 microdeletion by FISH analysis. Neither of the latter two authors commented on this particular finding as a possible manifestation in the CATCH 22 spectrum. The three patients of the present report constitute further examples of laryngeal atresia type III due to a de novo 22q11.2 microdeletion. It is of interest that patient 1 and 2 did not present with the "classical" facial phenotype of DGS or VCFS. However, the cardiac anomalies and the bilateral choanal atresia of patient 1 could also be considered as characteristic of the CHARGE syndrome. Although it is difficult to define minimal diagnostic criteria of the CHARGE syndrome, a few cases with 22q11.2 microdeletion have been classified as CHARGE [Clementi et al., 1991; Emanuel et al., 1992]. Furthermore, gastro-esophageal reflux has been described in patients with 22q11.2 deletions. In a series of 52 patients, McDonald-McGinn et al. [1995] found three cases with significant reflux. In conclusion, our findings confirm that laryngeal atresia type III in combination with other congenital malformations, especially cardiac defects, should definitely raise the suspicion of a 22q11.2 microdeletion.

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